Remarks

Double Patenting Rejection

Claims 20, 21 and 35-37 were rejected as claiming the same invention as claims 48, 50, and 51 of U.S.S.N. 08/268,809. It is believed these claims were previously cancelled but in the event they were nto, cancellation is again requested.

Rejections under 35 U.S.C. 112

Claims 48-51 were rejected as claiming subject matter which was not disclosed, specifically that page 27, lines 5-16 does not describe a method for making antibodies to solubilized, delipidized, reduced lipoproteins, arguing that the further requirements must be included: carboxymethylated and purified by gel electrophoresis, and that the antibodies must be monoclonal. The claims were also rejected on the basis that claim 48 fails to provide sufficient steps to produce antibodies. These rejections are respectfully traversed if applied to the amended claims.

The claimed invention is not the discovery of how to make antibodies or even a particular type of antibodies, specifically monoclonal antibodies. As the Examiner correctly notes, methods for making antibodies generally, monoclonal antibodies and even recombinant antibodies are well known to those skilled in the art. The invention is the preparation of an immunogen which can be used to generate antibodies to apolipoproteins and lipoproteins which is reactive independent of lipid content and conformation. The claims have been amended to more clearly define the method as including the steps of delipidating, reducing,

carboxymethylating, and solubilizing the immunogen, followed by purification to remove aggregated and degraded material resulting from the process. Support for these amendments is found in the application at pages 27, lines 8-10 and 47, lines 14-17. The claims have not been limited to gel electrophoresis since many equivalent methods are known to those skilled in the art to remove aggregates and degraded material, and the claims would be meaningless if they were so easily circumvented. Another method of purification is described at page 43 of the application. Others are described in the art cited by the examiner.

The claims have also not been all limited to production of monoclonal antibodies. The claimed method is a method to make antibodies generally to a modified immunogen. One cannot get monoclonal antibodies until one has first generated polyclonal antibodies by immunization with an antigen. Monoclonal antibodies are then generated by fusing individual B cells from the immunized animal with cultured cells to produce hybridomas, which are separated into single clones and then selected for based on antigen reactivity, as described in the application at page 16. By acknowledging that monoclonal antibodies are described, one has therefore recognized that making polyclonal antibodies is also described.

With regard to "omitted steps", the claimed method is to make antibodies. While it is certainly true that one would then isolate the antibodies and then screen them for specificity, and for commercial application, make monoclonal antibodies which would then be used in the diagnostic methods claimed in the related applications, this is not a critical step in the production of the antibodies per se, where the invention resides in the treatment of the immunogen which is

critical to production of antibodies which are reactive with the apolipoprotein or lipoprotein independently of lipid content or conformation.

The claims have also been rejected on the basis that the specification does not generally disclose the applicability of the method, being actually reduced to practice only for Apo B100. This rejection is respectfully traversed. The application contains a lengthy description of the different apolipoproteins and lipoproteins to be detected using antibodies. The method for solubilization, reduction, carboxymethylation and degree of purification are substantially the same for the different apolipoproteins and lipoproteins. One skilled in the art would be able to apply the same method demonstrated in example 2, page 47, for Apo B100, for the other lipoproteins and apolipoproteins described in example 1 at page 43, line 22 to page 47 (and also at page 23, line 29 to page 24, line 28): Apo AI, Apo AII, Apo CII, Apo E, chylomicrons, VLDL, LDL, and HDL. Recombinant antibodies are described in example 12, pages 70-74, using the same apolipoproteins and lipoproteinas as in example 1.

Testing for specificity of the antibodies is described in the application at page 16, line 31, to page 18, line 15.

The examiner cites no art nor provides any basis for arguing that these proteins are so different that one skilled in the art would not be able to apply the same method actually demonstrated using Apo B100, to these other apolipoproteins and lipoproteins with undue experimentation. The Court of Appeals for the Federal Circuit has repeatedly stated that mere assertions of insufficiency will not support a rejection under 112. Moreover, it appears that the

rejection is actually a rejection for lack of utility, and here again, there is nothing other than allegation in support of such rejection.

The Examiner is also respectfully reminded that this issue was extensively discussed with the examiner at the interview with Dr. Koren and Richard Schwartz some two years ago now, and it was the understanding of the other parties that scope of the claim was no longer an issue.

Rejections under 35 U.S.C. §102(b)

Claim 48 was rejected under 35 U.S.C. §102(b) as disclosed by Fuo, et al., J. Lipid Res. 30, 23-37 (1989). Claims 48, 50 and 51 were rejected under 35 U.S.C. §102(b) as disclosed by Zhou, et al. Acta Acad. med. Hubel, 11(4), 298-302 (1990). These rejections are respectfully traversed if applied to the amended claims.

As discussed above, the claims have been amended to require that the immunogen be delipidated, reduced, carboxymethylated, and solubilized. None of the cited art discloses all of these elements, and therefore cannot disclose the method as defined by the amended claims.

Guo, et al., discloses purification of a reduced and solubilized apolipoprotein at page 25. The SDS is totally insufficient to remove the lipid, although it is effective to solubilize the protein. There is no carboxymethylation step.

Zhou, et al., describes a procedure for purification of Apo AI using acetone-ethanol extraction to remove lipid, dissolution in urea, and purification by gel electrophoresis. There is no carboxymethylation, nor recognition of the need for such a step.

Proteins such as Apo B contain a number of free SH groups that can easily undergo oxidation under ordinary lab conditions. This can lead to inter- and intra-molecular crosslinking and masking or modification of a number of epitopes including the stable lipid independent epitopes. To expose these epitopes to the immune system to make antibodies, one must both reduce and carboxymethylate the protein to minimize the chance the epitope will not be exposed.

Rejections under 35 U.S.C. §103

Claims 48-51 were rejected under 35 U.S.C. §103(a) as obvious over Zhou, et al., Acta Acad. med. Hubel. 11(4), 298-302 (1990) in combination with Gooding, J.W. in Monoclonal Antibodies, Academic Press Inc. Orlando, FL pp. 56-97 (1983). Claims 48, 50, and 51 were rejected over Zhou, et al., in combination with Mills, et al. in Laboratory Techniques in biochemistry and molecular biology, a guidebook to lipoprotein technique, Elsevier, pp. 384-448 (1984). These rejections are respectfully traversed if applied to the amended claims.

As discussed above, the art fails to disclose preparation of an immunogen as defined by the amended claims. Moreover, the art fails to recognize that the presence of free sulfhydral groups in the solubilized, reduced, and delipidated issue would alter the type of antibodies made to the immunogen, i.e., decrease or prevent formation of antibodies that react with the protein regardless of lipid being bound to the protein or the conformation of the protein. Therefore the claimed method is not obvious even in view of the combination of cited references.

Allowance of all claims 43-46, as amended, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an appendix for the convenience of the examiner.

Respectfully submitted,

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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the U.S. Postal Service in an envelope with sufficient first class postage and addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on the date shown below.

Patrea Pabst

Date: November 3, 2000

APPENDIX: Claims as Pending upon entry of the amendment

43. (amended) A method for making an antibody to an epitope of an apolipoprotein or lipoprotein which reacts with the apolipoprotein or lipoprotein independently of lipid content and conformation of the apolipoprotein or lipoprotein, comprising

immunizing an animal with the apolipoprotein or lipoprotein which has been delipidated, reduced, carboxymethylated, solubilized, and purified to remove self-aggregated and degraded material from the delipidated, reduced, carboxymethylated, and solubilized apolipoprotein or lipoprotein.

44. The method of claim 43 further comprising

isolating the spleen from the immunized animals,

producing hybridomas from the spleen, and

screening the hybridomas for binding to the desired apolipoprotein or lipoprotein.

45. The method of claim 43 for making antibodies to an apolipoprotein wherein the apolipoprotein is selected from the group consisting of Apo AI, Apo AII, Apo B, Apo CIII, and Apo E.

46. The method of claim 43 for making antibodies to a lipoprotein wherein the lipoprotein is selected from the group consisting HDL, LDL, and VLDL.